Long term follow up of the NCRI AML17 Trial of attenuated Arsenic Trioxide and ATRA therapy for newly diagnosed and relapsed Acute Promyelocytic Leukaemia

Nigel Russell[1] Alan Burnett[2], Robert Hills[3], Sophie Betteridge[3], Mike Dennis [4], Jelena Jovanovic[5] Richard Dillon[5], David Grimwade[5] on behalf of the NCRI AML Working Group

1 Centre for Clinical Haematology, Nottingham University Hospitals NHS Trust, Nottingham, UK

2 Blackwaterfoot, Arran, Scotland, UK

3 Centre for Trials Research, Cardiff University, UK

4 Department of Haematology, Christie Hospital, Manchester , UK

5 Department of Medical and Molecular Genetics, Kings College Medical School, London, UK

We have previously reported on the results of the NCRI AML17 Trial which for APL compared Anthracycline/ATRA (AIDA) vs the combination of Arsenic Trioxide (ATO) +ATRA which utilised an attenuated schedule of ATO[1]. Here we present long term survival results for randomized patients and for 32 patients who received the same schedule of ATO + ATRA after relapsing from the AIDA arm. Ethics approval was provided by Wales REC 3, and all participants provided signed informed consent. From May 2009 to October 2013, 235 patients aged >16 years were randomized to either ATRA+ATO (8 week induction 0.3mg/kg d1-5 w1, 0.25mg/kgx2/w w2-8, followed by 4 consolidation courses of 0.3mg/kg x2 w1, 0.25mg/kgx2/ w2¬4 (63 ATO doses) or AIDA schedule: Idarubicin (Ida)12mg/m2 d2,4,6,8 + ATRA to d60) (induction) then Ida 5mg/m2 d1-4 + ATRA d1-15 (Course 2); Mitoxantrone. 10mg/m2 d1-4 + ATRA d1-15 (course 3); Ida 12mg/m2 d1 + ATRA d1-15 (Course 4). ATRA was 45mg/m2/d in 2 divided doses. Maintenance was not given. High risk patients could receive a single dose of Gemtuzumab Ozogamicin (d1, 6mg/m^2). In addition another 70 patients were treated in AML17 with AIDA after closure of the randomization and were available for the analysis of ATO at relapse. Of the 189 patients treated with AIDA, 33 relapsed and 32 were treated with the same attenuated schedule of ATO + ATRA receiving a median of 4 cycles (range 1-5). Follow-up is complete to 1 July 2017.

The median age was 47y (16-77); 57 had WBC>10x109/L (27 AIDA, 30 ATRA+ATO) and 49 (24 AIDA, 25 ATRA+ATO) were >60y. The early results of the randomization for newly diagnosed patients have been reported and have not changed. 91% entered morphological CR with no significant difference in CR rate between the arms (Chemo-free 94%, AIDA 89%; OR 0.54 (0.21-1.34), p= 0.18). With a longer median follow-up of 67.4 months the 5-year survival is now 92% (chemo-free) v 86% (AIDA) (HR 0.71 (0.33-1.50) p=0.4; Figure 1A). Among patients who became MRD negative, molecular relapse free survival is 97% vs 78% (HR 0.25 (0.12-0.52) p=0.0002; Figure 1B). No patient treated with ATRA+ATO who became molecularly negative relapsed; among AIDA treated patients, 5-year cumulative incidence of any relapse (including molecular) was 20%. A significant

reduction in frank relapse (1% vs 10% at 5 years, HR 0.18 (0.05-0.60) p=0.005)) translates to a better RFS for the chemo-free approach (96% vs 86%, HR 0.43 (0.18-1.03) p=0.06; Figure 1C); the results are not affected by risk group (low risk 95% vs 87%, HR 0.58 (0.22-1.55) p=0.3; high risk 100% vs 83%, HR 0.12 (0.02-0.84) p=0.03; test for interaction p=0.16). With additional follow-up the molecular relapse risk with AIDA is higher than that observed in our previous AML15 trial (20% v 9%) where maintenance was employed[2] however the incidence of secondary AML/MDS was less in AML 17 (1% v 6%). No cases of secondary AML/MDS were seen after ATO +ATRA.

Of the 32 patients who relapsed following AIDA therapy, 1 died in frank relapse before treatment could be initiated and 31 (5 with concomitant CNS involvement) were treated with the attenuated ATO schedule. Of these 17 were treated at molecular relapse, reflecting the value of centralised MRD monitoring stipulated in the protocol. All 31 patients achieved molecular CR of whom 5 patients received additional consolidation therapy with high dose cytarabine (n=4) or Gemtuzumab ozogamicin (n=1) after achieving molecular remission. Of these 5 patients, 1 had a haematological relapse and 3 a combined haematological and CNS relapse. 13 patients were transplanted in CR2 (10 autograft, 3 allograft) including 4 of the 5 patients with CNS disease and the 5 patients who had received additional chemotherapy. Of the 18 patients treated with ATO +ATRA alone without transplant or consolidation chemotherapy, 14 remain in molecular remission and 4 have relapsed (molecular in 3) With median follow-up from relapse of 44.9 months, the 5-year overall survival for all 31 patients is 88% with two deaths, both in transplanted patients; one 37 months post-allograft in second molecular remission, the other 36 months post-autograft in a patient who suffered a second molecular relapse post-transplant, and then achieved a third remission. This patient had received only 1 course of ATO prior to autograft.

Genomic DNA was available from 31 patients who relapsed; paired diagnosis and haematological relapse samples were available from 8 patients and diagnostic material only from a further 23. We performed targeted next-generation sequencing of a panel of 60 genes frequently mutated in AML. Molecular barcoded libraries were prepared using the HaloPlexHS sytem and sequenced using an Illumina HiSeq 2500 instrument. Alignment and variant calling was performed using Agilent SureCall v4 software. In parallel we

performed PCR and fragment analysis to detect the FLT3 internal tandem duplication as previously described.[3]. In keeping with previous reports, FLT3 ITD was the most frequent mutation and was detected in 14/31 patients (45%). Other recurrently mutated genes were WT1 in 7 patients (23%) NRAS in 3 (9.6%) and RUNX1 and KRAS in two patients each (6.4%). Profiling of the 5 patients who relapsed post salvage ATO 2 showed no consistent findings, 2 had FLT3 ITDs, 1 had NRAS/KRAS mutations, 1 had a WT1 mutation and 1 had no mutations suggesting that the relapses post ATO are not predictable based on upfront genomic data.

The primary purpose of this updated analysis was to establish if an overall survival benefit for the ATO+ATRA has emerged as has been reported in the pivotal randomised APL0406 trial conducted in Italy and Germany by the GIMEMA, AML Study Group (AMLSG) and Study Alliance Leukaemia (SAL) cooperative groups [4, 5] In AML17 although we found that the combination of ATO and ATRA continues to show a very low risk of relapse irrespective of risk group resulting in significantly reduced molecular and haematological relapse, and better RFS compared to AIDA no overall survival benefit has emerged. These results are supported by a recent report from Abaza et al (2016) who also observed a low relapse risk in both standard and high risk APL patients treated with ATO plus ATRA supplemented by Gemtuzumab Ozogamicin (GO) in high risk patients [6] In that study 46% of standard risk patients also received GO as treatment of leucocytosis an intervention we used in only 6% of patients suggesting that GO makes a minimal contribution to the low relapse risk with ATO at least in standard risk disease.

In AML17 the lack of survival benefit resulted from the highly effective salvage intervention for AIDA-treated patients with ATO with the majority of patients treated at molecular relapse. Molecular monitoring for t(15;17) is therefore essential to optimize therapy with AIDA. For patients treated with first line ATO and ATRA molecular monitoring is of questionable value once molecular CR has been documented, but molecular surveillance remains important in those with relapsed disease. The attenuated AML17 ATO dosing was effective both as first line therapy and in relapsed patients resulting in a sustained anti-leukemic efficacy. These results also question the role of transplantation as consolidation for relapsed patients as has been recommended [7] at least in patients

achieving molecular remission with ATO and ATRA who do not have CNS disease at relapse and who have received a full course of consolidation with ATO.

Acknowledgments

This trial was sponsored by Cardiff University (Cardiff, UK). We thank Cancer Research UK for providing research support for the trial; Cephalon and Teva for providing arsenic trioxide; the main investigators and colleagues who enrolled patients; Guy's & St Thomas' Hospital (London, UK) for curation of the molecular monitoring database; and the Haematology Cancer Trials Unit at Cardiff University

References

1. Burnett AK, Russell NH, Hills RK et al. Arsenic trioxide and all-trans retinoic acid treatment for acute promyelocytic leukaemia in all risk groups (AML17): results of a randomised, controlled, phase 3 trial. Lancet Oncol 2015; 16: 1295-305..

2. Burnett A K, Hills R K, Grimwade D. et al. Inclusion of chemotherapy in addition to anthracycline in the treatment of acute promyelocytic leukaemia does not improve outcomes: results of the MRC AML15 trial. Leukemia 2013; 27 (4):843-85.

3. Kottaridis PD, Gale RE, Frew ME et al. The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials. Blood 2001;98(6):1752-9

4. Lo-Coco F, Avvisati G, Vignetti M et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N.Engl.J.Med. 2013; 369 (2):111-121.

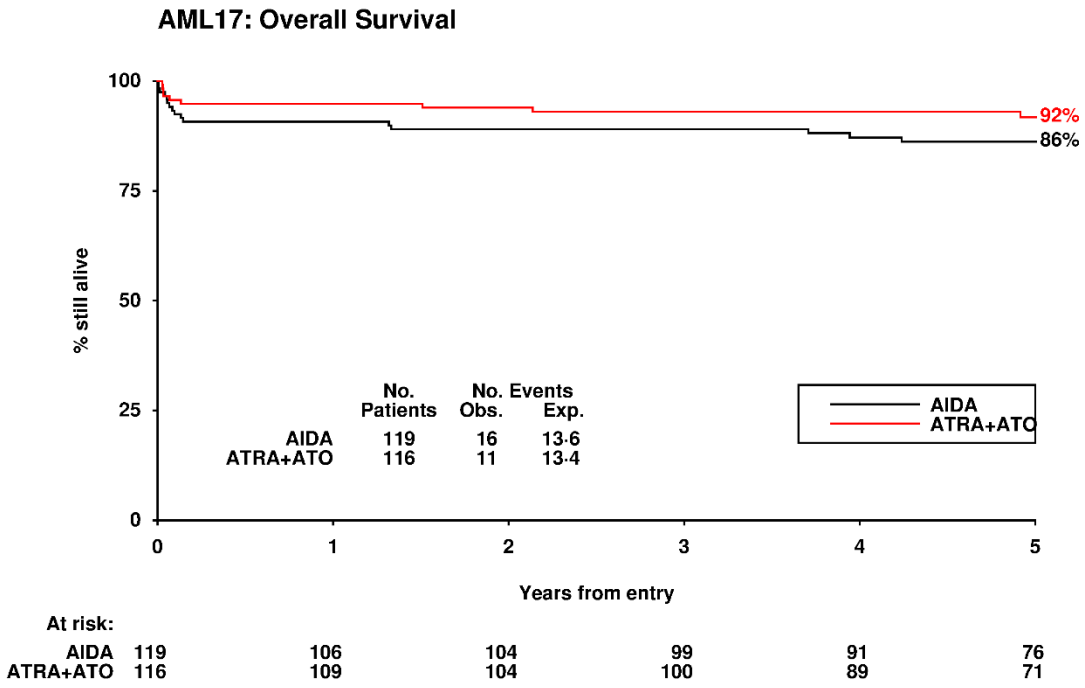
5. Platzbecker U, Avvisati G, Cicconi L et al. Improved Outcomes With Retinoic Acid and Arsenic Trioxide Compared With Retinoic Acid and Chemotherapy in Non-High-Risk Acute Promyelocytic Leukemia: Final Results of the Randomized Italian-German APL0406 Trial. J Clin Oncol 2017,35, 606-612.

6. Abaza Y, Kantarjian HM, Garcia-Manero G et al. Long-term outcome of acute promyelocytic leukemia treated with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab. Blood 2017 129:1275-1283

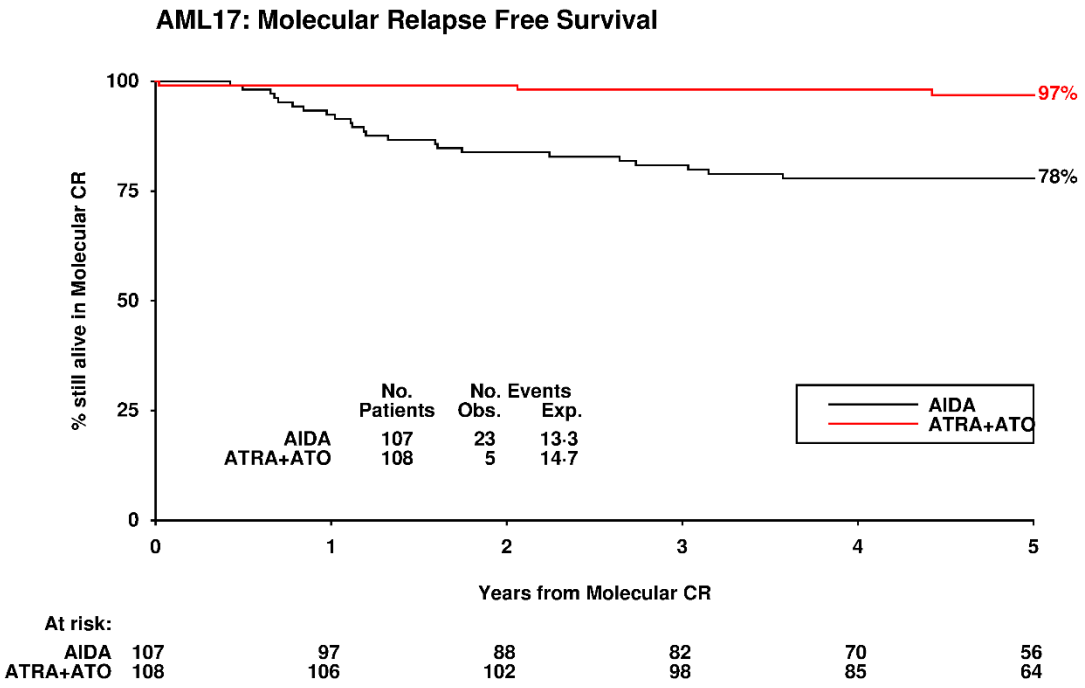
7. Sanz, M.A., Grimwade, D., Tallman, M.S., et al. Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. Blood, 2009 113, 1875–1891;

Figure 1: Clinical Outcomes: A) Overall Survival for chemo-free vs AIDA approach; B) Molecular relapse free survival; C) Relapse Free Survival; D) Survival from relapse for relapsing AIDA patients treated with ATRA+ATO split by transplantation

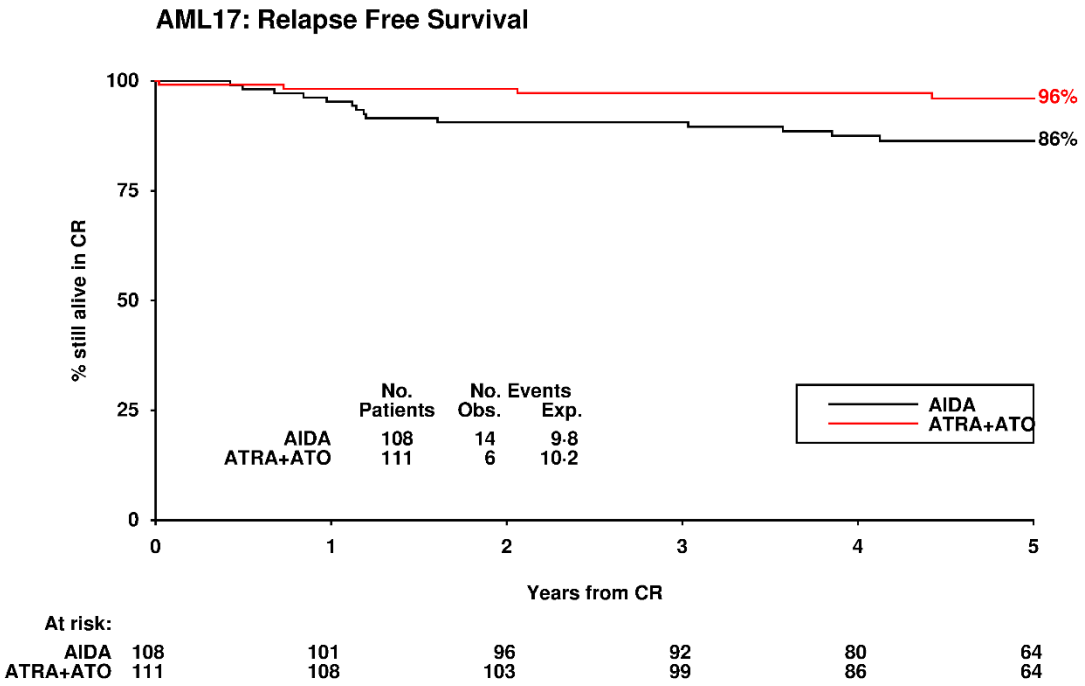
a)



b)



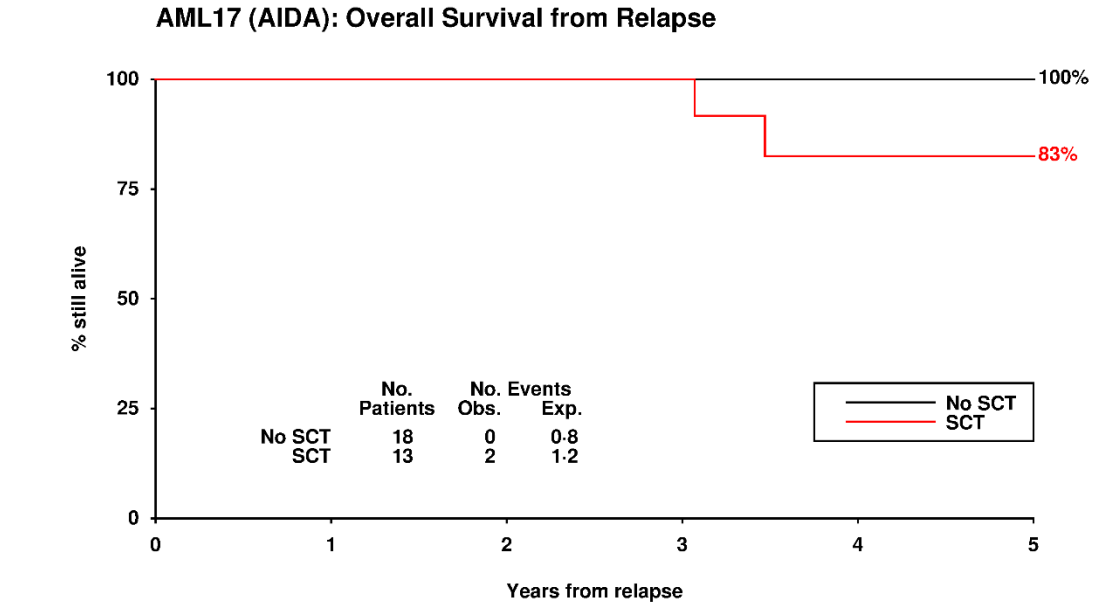
c)



At risk:

AIDA	108	101	96	92	80	64
ATRA+ATO	111	108	103	99	86	64

d)



At risk:

No SCT	18	17	15	8	4	1
SCT	13	13	13	12	7	1